



Increased Dementia and Mild Cognitive Impairment (MCI) by Impaired Glucose Metabolism

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Abbreviations: AD: Alzheimer's Disease; MCI: Mild Cognitive Impairment; LCD: Low Carbohydrate Diet; T2DM: Type 2 Diabetes Mellitus; PAF: Population Attributable Fraction; DASH: Dietary Approaches to Stop Hypertension

Introduction

Diabetes has been evaluated as a key risk factor for mild cognitive impairment (MCI) and dementia [1-3]. Then, increasing the prevalence of diabetes and prediabetes would contribute the burden of MCI and dementia in the healthcare systems in each country [4]. Consequently, the links between diabetes, MCI and dementia would be investigated for the improvement of these diseases in the future [5].

A metabolic state that exists between normal glucose variability and type 2 diabetes mellitus (T2DM) would be defined as prediabetes. Recently the ratio of the prediabetes in adult has been rapidly increasing, which would be estimated as about 35% in the USA and UK, and up to about 50% in China [6].

Across the world, approximately 47 million people were suffering from dementia in 2015, and this number is estimated to triple by 2050 [2]. Furthermore, the global cost of dementia in 2015 was probably to be US\$818 billion, and this figure will be increased as the subjects with dementia will rise [2].

There have been several statistic data about dementia and diabetes. T2DM patients for 5 years or more tend to show increased dementia risk of 40-60% [7]. The risk for dementia seems to be increased for higher mean blood glucose in the patients less than 84 years old. The treatment of not insulin, but oral hypoglycemic agents would lead to lower risk of developing dementia [7]. Furthermore, hypoglycaemia seems to show a bi-directional association with cognitive impairment [8].

T2DM has been evaluated to increase the risk for cognitive dysfunction across all cognitive domains. The relative risks of

developing dementia and vascular dementia in people with T2DM would be 1.51 and 2.48, respectively [9].

Increased dementia risk in general people was believed to be associated with elevated blood cholesterol values. For T2DM patients, however, there are discrepancy of the ratio for dyslipidemia in the case of both of increased or decreased risks of cognitive impairment [10]. After that, cholesterol values do not influence the risk of progression from MCI to dementia [1].

Certain relationship exists between glucose variability and Alzheimer's disease (AD). When the patient has already established AD, the level of cognitive impairment has been correlated with the reduced level of glucose uptake. Moreover, some evidence was found that changed energy metabolism in the brain would induce the development to the level of AD [11,12].

There are three kinds of ketone bodies (KB), which are produced from fat metabolism in the body. Among them, 3-OHBA (3-hydroxybutyric acid) and AcAc (acetoacetic acid) have the function of KB. They can be used for production of the energy, and the energy is consumed in brain and muscle.

From pathophysiological mechanism of AD, various approach to the nutrition therapy for AD would become crucial problems in the future. The reason is that AD has been associated with impaired glucose metabolism from various research so far [11]. Further, insulin resistance and impaired insulin secretion would be also significant problem for AD [13].

There have been many kinds of nutritional therapy introduced so far. Among them, they can be generally divided into two categories,

which are low carbohydrate diet (LCD) and calorie restriction diet (CRD) in the diabetic medical practice. On the other hand, in the field of management of dementia and MCI, the recommended and rather popular regimens would be the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets [14].

For the prevention of AD, dietary recommendation would be the similar to that of diabetes, and diseases of metabolic syndrome [15]. Among them, Mediterranean diet would be beneficial type of nutrition therapy because of its lower risk rate of AD.

There are several modifiable risk factors for dementia. For the study on dementia risk, midlife life would be 45-65 years old, and later life would be older than 65 years [2]. The research was focused on estimating the population attributable fraction (PAF). It is the reduction ratio in new cases for a certain period if one risk factor was completely distinguished. There have been several related factors such as diabetes, hypertension, obesity, physical inactivity, smoking depression and low educational attainment [16]. Potentially modifiable risk factors for dementia in later life more than 65 years old was calculated. Those data of relative risk were that smoking 1.6, depression 1.9, physical inactivity 1.4, social isolation 1.6, and diabetes 1.5. Among them, total weighted PAF adjusted for communality was 35% [2].

Furthermore, a systematic review and meta-analysis for social isolation and incident dementia were applied to calculate its PAF [17]. It included social contact (telephone or face-to-face contact), social participation (participation in community activities) and loneliness (feeling at dissatisfaction from social contact). The value of weighted relative ratio (RR) for incident dementia from less frequency of social contact was 1.57 [17].

In recent years, depression is one of the important problems. Patients with T2DM has been estimated to have depression up to 39% [18]. Further, those people with T2DM and depression will have twice as likely to become dementia.

On the other hand, diabetic patients have been increasing so far and estimated to be approximately 700 million by 2045 [19]. Several controversies have been found about the diet therapy such as LCD and CRD through various clinical research for long years. There have been some guidelines from American Diabetes Association (ADA) and American College of Physicians (ACP) in recent years, in which the evaluation and management for HbA1c and the goal have some difference [20].

For diabetic therapy, LCD has been applied and known in European countries so far. On the other hand, LCD has been initiated by authors and co-researchers and developed through lectures and books [21]. There are three useful kinds of LCD including petite, standard and super [22]. Further, we have reported clinical significance of role for Ketone Bodies (KB) in the axis of fetus-placenta-newborn-mother and in the situation of clinical LCD continuation [23].

Summarized mentioned above, diabetes has been risk factor of dementia and MCI. These diseases have been increased and

become medical and social problem across the world. This article would be a reference for future research and clinical practice.

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